REMARKS

Claims 1 – 3 and 5 - 21 are currently pending in the application. No claims are presently withdrawn from consideration. Claims 2 and 8 are cancelled. Claims 1, 3, 9 and 11 are amended. No new claims are added. No new matter has been added. Support for the amendments can be found throughout the claims and specification, for example at page 9.

Objections

The Examiner has objected to the oath or declaration because it was not executed in accordance with either 37 CFR 1.66 or 1.68. The Examiner has requested that a new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date be filed. Applicants submit herein the required documents and respectfully request withdrawal of the objection.

The Examiner has objected to claims 11 and 12 for minor informalities requiring clarification. Applicants point out that claim 12 was previously withdrawn. Applicants have amended claim 11 to clarify that some members of the repertoire are at least partially unfolded. Applicants respectfully request withdrawal of the objection.

The Examiner has objected to claim 2 as being of improper dependent form for failing to further limit the subject matter of claim 1. Applicants have cancelled claim 2 and respectfully request withdrawal of the objection. The dependency of claim 3 is amended in view of the cancellation of claim 2.

The Examiner has objected to claim 8 as being of improper dependent form for failing to further limit the subject matter of claim 1. Applicants have cancelled claim 8 and respectfully request withdrawal of the objection.

Rejection of Claims 1 –3, and 5 - 21 Under 35 U.S.C. §112, first paragraph

Written Description

Claims 1 – 3 and 5 – 21 are rejected under 35 U.S.C 112 as failing to comply with the written description requirement. Applicants respectfully traverse the rejection.

The Examiner argues that the invention as claimed encompasses all known fusion proteins and all potential fusion proteins since virtually any protein can be cleaved. The Examiner alleges that, "the claimed invention does not include any structural information regarding folding of the polypeptide that could prevent cleavage of any cleavage agent (Office Action, p.6)." Applicants disagree. On p. 5, lines 28 – 30 and p. 6, lines 20 - 30, the specification teaches the position of the cleavable site in the virus. Further, Applicants direct the Examiner to the definition of "cleavable site" in the specification at p. 4, lines 19 – 26, wherein:

> A feature of the cleavable site is that it should either be absent from the virus other than at the site of its specific insertion according to the present invention, or otherwise inaccessible to cleavage, or present only in viral proteins which are not required after virion assembly to mediate infection."

The Examiner argues that the claimed invention does not include the structural limitations of the particular residues or structural limitations regarding how the cleavage sites are made inaccessible. However, on p. 9 lines 15 – 26, the specification teaches both how the protease cleavage sites may be incorporated into the coat protein of a virus, and where the protein should be inserted:

> Protease cleavage sites may be incorporated into the coat protein of a virus by constructing a fusion between the coat protein and a further polypeptide, the further polypeptide containing the cleavage site. The further polypeptide should be inserted at a position in the viral coat protein such that it allows the assembly of a functional viral capsid and subsequent infection, but if cleaved will result in the impairment of infectivity.

The Examiner acknowledges that the specification teaches at page 9 a number of examples of proteases that are useful as the cleaving agent according to the invention (p. 6 – 7, Office Action) and even acknowledges that the specification teaches at p. 9 specific cleavage residues of the proteases:

> Preferred cleavable sites include protease-cleavage sites, which may be found in polypeptides or engineered as an integral part of their sequence. Typically, protease cleavage sites may be defined in terms of amino acid sequences which are susceptible to cleavage by a protease. For example, the invention encompasses the use of protease cleavage sites cleavable by one or more of the proteases trypsin (cleaves at Lys, Arg),

chymotrypsin (Phe, Trp, Tyr, Leu), thermolysin (small alipathic residues), subtilisin (small alipathic residues), Glu-C (Glu), Factor Xa (Ile/Lue-Glu-Gly-Arg), Arg-C(Arg) and thrombin. (p. 9, lines 5 – 14)

Further, Applicants have amended claim 1 to specify that the cleaving agent is a protease that recognizes said cleavable site. As described herein, Applicants have provided a reasonable representation of cleaving agents, and Applicants have provided teaching of where the cleavable site should be located. Applicants have provided detailed examples directed to the invention as claimed.

As such, Applicants respectfully request withdrawal of the written description rejection and allowance of the claims.

Enablement

The Examiner has rejected claims 1 – 3 and 5 – 21 under 35 U.S.C. §112, first paragraph. The Examiner asserts that while the specification is enabling for a method of selection of a virus comprising providing a virus encoding and displaying barnase mutant A or villin with a cleavage site, exposing the virus to cleaving agents and propagating the virus in a manner that makes the cleavage site inaccessible, the specification does not "reasonably provide enablement for a method of selection of a virus utilizing any known or unknown cleavage site, any known or unknown cleavage agent, and any known or unknown polypeptide." Applicants respectfully disagree and traverse the rejection.

Applicants have amended claim 1 to specify that the cleaving agent is a protease that recognizes the cleavable site. The amended claims are drawn to a method for the selection of a virus comprising the steps of providing a virus comprising a plurality of virions encoding and displaying a fusion polypeptide, the fusion polypeptide comprising a heterologous polypeptide inserted into the sequence of a viral coat protein polypeptide, wherein the plurality of virions comprise a cleavable site located within the displayed polypeptide and wherein cleavage of said cleavable site impairs infection by a said virion, and exposing the virus to a protease that recognizes the cleavable site, wherein said protease only cleaves said cleavable site if said fusion polypeptide is not properly folded, and propagating a virion comprising intact fusion

polypeptide. One of skill in the art, given the disclosure of the instant specification and the level of knowledge and skill in the art, would be able to perform the invention as claimed.

As stated in the MPEP at § 2164.01(a):

> There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:
>
> (A) The breadth of the claims;
> (B) The nature of the invention;
> (C) The state of the prior art;
> (D) The level of one of ordinary skill;
> (E) The level of predictability in the art;
> (F) The amount of direction provided by the inventor;
> (G) The existence of working examples; and
> (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The Examiner argues that the claims include "any virus that can express a fusion polypeptide...any cleavage site regardless of specificity for a particular cleaving agent...(and) any cleaving agent (Office Action p. 9). The claims, as amended, are drawn specifically to protease cleaving agents. Moreover, the Specification provides examples at page 9, lines 5 - 14 of what the proteases can be, and where they will cleave:

> trypsin (cleaves at Lys, Arg), chymotrypsin (Phe, Trp, Tyr, Leu), thermolysin (small alipathic residues), subtilisin (small alipathic residues), Glu-C (Glu), Factor Xa (Ile/Lue-Glu-Gly-Arg), Arg-C(Arg) and thrombin.

The specification has provided clear guidance for one of skill in the art to choose a protease, and know what the target sequences of those proteases will be, for use in accordance with the invention.

The Examiner alleges that the state of the art "is silent at the time of the disclosure with regard to correlating a decrease in viral infectivity with improper protein folding including which cleavage sites and agents would be advantageous in the method (Office Action, page 10)." The Examiner cites the Kristensen et al. reference as teaching that "a cleavage site with several proteolytic sites was susceptible to cleavage by trypsin, thermolysin, subtilysin, Glu-C and

chymostrypin, but infectivity of the virus was not altered by factor Xa, Arg-C, or thrombin even though potential cleavage sites were present (Office Action, page 10)." However, the Kristensen et al. reference goes on to teach that if a flexible linker is inserted between domains D2 and D3 of the phage coat protein p3, the phage becomes sensitive to cleavage. See, for example, p. 322 and Figure 1. The Examiner also cites the Sieber et al. reference as allegedly teaching towards the unpredictability in the art; however the Sieber et al. reference is drawn to a method, "Proside," which involves "several cycles of in vitro proteolysis, infection and phage propagation" to enrich for the most stable variants. The Sieber et al. reference teaches a specific method of selection for stabilized variants of a protein; however contrary to the Examiner's argument that the method is best suited for monomeric proteins, the reference states that the Proside method "should be generally applicable to globular proteins provided that a large repertoire of sequences can be generated (p 958, column 2)." Thus, the Sieber et al. reference does not teach away from methods of correlating proteolytic stability with either monomeric or globular proteins.

The Examiner argues that Example 2 teaches unpredictability in cleaving agents that would be useful in the invention. Applicants disagree. Example 2 is an illustration of one embodiment of the invention. The specification teaches on p.9, lines 22 – 26, that:

> If the protease cleavage site incorporated in the coat protein remains uncleaved, therefore, the virus is capable of assembly into functional virions and retains the potential to infect host cells. If the protease cleavage site is cleaved, however, the structure of the viral coat protein will be compromised and the virus will lose at least part of its potential to infect host cells.

Turning to Example 2, the example teaches construction of a phage with protease cleavage sites (page 15, lines 13 – 24). As the Examiner points out, the Example teaches that:

> Incubation of the phage under native conditions with trypsin, thermolysin, or subtilisin now resulted in almost complete loss of infectivity...and incubation with Glu-C and chymotrypsin resulted in a major loss. This indicates that these proteases cleave the new linker. However incubation with Factor Xa, Arg-C or thrombin did not lead to loss in infectivity.

Example 2 teaches an important aspect of the claimed invention, that is that on the incorporation of a flexible linker containing a protease cleavage site between the D2 and D3 domains of the

phage coat protein ,p3, the phage becomes sensitive to cleavage (Example 3). Example 2 does not teach away from the predictability of the invention, but rather provides a logical step in the progression that one of skill in the art would need to take to perform the invention as claimed.

Finally, the Examiner acknowledges that Applicants have provided in the specification examples of two fusion proteins that can be utilized to make the cleavage site inaccessible via folding. The Examiner acknowledges that Applicants have provided example of one cleaveage site construct, and have provided examples of (eight) cleavage agents that would be useful for additional experiments (Office Action, p. 11). Applicants have pointed out to the Examiner why all eight cleavage agents as taught in Example 2 are useful in the claimed invention. Moreover, Applicants provide 6 working examples to illustrate the claimed invention. Thus, Applicants have provided ample direction and working examples to enable the invention as claimed.

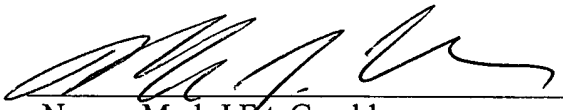
Based on the amended claims and arguments presented above, Applicants submit that one of skill in the art would be fully enabled to perform the invention commensurate in scope with the claims. Applicants respectfully request withdrawal of the rejection.

CONCLUSION

In view of the above amendments and remarks, Applicant believes the pending application is in condition for immediate allowance. Any additional fee occasioned by this paper may be charged, or overpayment credited to, Deposit Account 04-1105, Reference No. 208039/1090.

Respectfully submitted,

Date: January 3, 2007



Name: Mark J FitzGerald
Registration No.: 45,928
Customer No.: 29933
Edwards Angell Palmer & Dodge LLP
P.O. Box 55874
Boston, MA 02205
Tel: 617-239-0100